REMARKS

The Office action dated November 15, 2002 is acknowledged. Claims 1-15 are pending in the instant application. According to the Office action, claims 1-15 have been rejected. However, Applicant thanks the Examiner for the withdrawal of the rejections under 35 USC, first paragraph in the previous Office action. By the present "Reply to First Office Action," claims 1 and 15 have been amended and they, and the respective dependent claims, are now believed to be allowable. Reconsideration is respectfully requested in light of the amendments being made herein and of the following remarks. No new matter has been added.

Rejection of Claims 1-15 under 35 U.S.C. 103 (a)

Claims 1-15 have been rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,503,844 (Kwiatek et al.) in view of U.S. Patent No. 5,066,494 (Becher). It is respectfully submitted that these claims are patentably distinct from the prior art references, either alone or in combination.

Examiner states that Kwiatek et al. '844 teaches the use of a transdermal therapeutic patch for the controlled release of lovastatin to the skin or mucuous membranes and refers to col. 1, lines 54-67; col. 2, lines 1-40; col. 8, lines 12-65; col. 16, lines 58-67; col. 17, lines 1-14 and col. 24, lines 23-58. Examiner further states Kwiatek et al. '844 does not explicitly teach a patch in which the active substance is contained within a self-adhesive matrix layer, but rather one in a foam which requires a laminate to be affixed onto the skin or mucosa for the release of the active agent.

Examiner relies on Becher '494 because, according to the Examiner, it teaches a transdermal patch comprising a contact adhesive layer as a means of fixing the therapeutic system onto the human skin and refers to col. 2, lines 32-56 and col. 4, lines 1-27. Therefore, the Examiner concludes, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use a therapeutic patch delivery system consisting of an adhesive layer as a means for affixing the therapeutic composition onto the skin of a patient. This in turn, according to the Examiner, would result in a transdermal patch that adheres well to the skin and offers administration of the active substance.

Applicant respectfully points out that to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art references when combined must teach or suggest all of the claim limitations. Applicant respectfully states that even when Becher is combined with Kwiatek et al., each of the claim limitations of the present invention are not taught or suggested. Specifically, as explained below, a transdermal therapeutic system having a substantially constant sustained release over a 72-hour period is not taught or described. Nor is there taught or described the feature of the present invention that the transdermal therapeutic patch has a pressure-sensitive adhesive layer. Therefore, Applicant respectfully requests that the present rejection to claims 1 – 15 be withdrawn.

Applicant respectfully disagrees with the Examiner's conclusions set forth above. Applicant wishes to point out that one significant difference between the transdermal therapeutic patch of the present invention and those of the cited prior art is the manner of

incorporating the active substance into the matrix/reservoir. The patch of Kwiatek et al. '844 has the active substance contained in a foam and the patch of Becher '494 has the active substance contained in chambers within the matrix. Contrastly, the present invention has the active substance mixed with the matrix material and then cast to form a film layer (see examples as provided in the specification). Therefore, the active substance is incorporated within the matrix material rather than only in the matrix layer next to the matrix material. This feature is not described in either prior art reference, alone or in combination.

In addition, Applicant submits that the matrix material of the present invention is a pressure-sensitive adhesive material such that the resulting patch can be affixed to a patient's skin without having to provide an additional adhesive layer. However, both Kwiatek et al. '844 and Becher '494 teach that its respective transdermal therapeutic patch must be provided with an additional adhesive layer, in addition to the matrix or reservoir layer. This is because the material of the matrix/reservoir of either Kwiatek et al. '844 or Becher '494 is not a pressure-sensitive adhesive material.

Claims 1 and 15 have been amended to clearly define the matrix as comprising a mixture of the active substance and the self-adhesive polymer. This was previously stated in slightly different words in earlier versions of these claims. (Claim 1 previously recited "A preparation containing at least one active substance..., wherein said preparation is present in the form of a transdermal therapeutic patch containing the active substance in a self-adhesive polymer matrix layer, said active substance being incorporated in the preparation to form the polymer matrix layer..."). Thus, no new subject matter has been added to the claims, and no matter was removed therefrom.

The Examiner had also noted in the present Office action that the Applicant, in the response to the Office action dated May 20, 2002, has not shown that the transdermal formulation of the prior art is not capable of providing sufficient adhesive qualities, such as a constant release rate over a 72-hour period, and achieving the same results therewith. Applicant respectfully refers the Examiner to tables I and III of Kwiatek et al. '844 which provide data for the release kinetics of nicotine over a 24-hour period. The data in these tables clearly show that the transdermal patch of Kwiatek et al. is unable to provide a constant release of active substance over a 72 hour period. Applicant herewith has prepared the tables in an alternative format to even more clearly demonstrate the above conclusion.

Table I

Nicotine In-Vitro FLUX Through Skin (mg/10 cm^2 X hr)

	2 hr. period	4 hr. period	9.5 hr. period	24 hr. period
Example	0.545	0.6525	0.583	0.365

Table III

Nicotine In-Vitro FLEX Through Skin (mg/10 cm^2 X hr)

	2 hr. period	4 hr. period	8 hr. period	24 hr. period
Example 2	0.31	0.315	0.2675	0.195
Example 3	0.435	0.445	0.406	0.321
Example 4	0.54	0.5825	0.406	0.48

The above tables demonstrate that the average hourly release of active substance from a patch of Kwiatek et al. during a 24 hour period is significantly lower at the end of the 24-hour period than during the initial 2 hour or 4 hour period. Because the hourly release at the beginning of the 24th hour of any given 24 hour period is not as high as the hourly release in that period's respective initial 2 hour or 4 hour period, it appears that the release rate at the end of the 24 hour period would be even lower than the average release during the entire period. This leads one to the conclusion that the patch according to Kwiatek et al. '844 is unable to provide an essentially constant release rate over a 24 hour period of time. If it can not provide a constant release rate over a 24 hour period of time, then it would follow that the patch of Kwiatek et al. can not provide a substantially constant release rate over a 72 hour period of time. Applicant wishes to note that although the data provided in Tables I and III of Kwiatek et al. '844 was acquired having used nicotine as the active substance, there is no indication at all in the reference that the results or release kinetics are a specific effect related to nicotine. There is no evidence therein that the release kinetics would be any different for other active substances such as HMG-CoA reductase inhibitors or any other substances having an influence on the levels of blood lipids, such as in the present invention.

Regarding Becher '494, it is Applicant's belief that the release kinetics of an active substance of a patch according to this reference would not differ from the release kinetics of a patch of Kwiatek et al. '844. This is because the concept of providing the active substance in the patches of the respective prior art references is essentially the same, both of which are fundamentally different from that of the present invention. Both

references teach that the active substance is provided in cavities formed by the polymer material of the reservoir. There can be either one or a few cavities, as disclosed in Becher '494, or many cavities present in the foam, as disclosed in Kwiatek et al. 844. Because of the aforementioned reasons, the patches of both prior art references do not allow or provide for a consistent dosage of an active substance over at least, or even less than, a 24 hour period.

Referring now to the present invention, Applicant additionally submits that it is the admixture of the active substance and the matrix polymer, as shown in the examples provided throughout the specification, which allows for an essentially constant release of the active substance over a long period of time, i.e. 72 hours. Neither Kwiatek et al. '844 or Becher '494 teach or disclose such an admixture, nor would the combination of the two render this feature of the present invention obvious.

In response to the Examiner's contention that the Applicant has not shown specific data to differentiate the present invention from either prior art reference, Applicant respectfully submits that it is not possible for an applicant to envisage all the prior art which will be considered during prosecution of the application. Therefore, it was not possible for the Applicant to know at the time of invention that it would have to prepare and provide specific data and examples to differentiate the 72 hour sustained release of the present invention from the patches taught in either Kwiatek et al. '844 or Becher '494 or to demonstrate the advantages thereof over either of the prior art references.

Applicant respectfully submits that even when Kwiatek et al. '844 is combined with Becher '494, each of the essential features of the present invention as recited in the claims are not taught or disclosed. That is, the combination still does not teach a transdermal therapeutic patch having pressure-sensitive adhesive layer or that the active substance is mixed with the matrix material and then cast to form a film layer. The combination of prior art references also still does not teach a transdermal therapeutic patch having a constant sustained release over a 72 hour period. Moreover, one skilled in the art would not have a reasonable likelihood of success to prepare a transdermal therapeutic patch having a constant sustained release over a 72-hour period by combining the cited prior art references since the combination would not provide a patch having a sustained release for over even a 24-hour period. Because each and every element of the present invention is not disclosed or taught by the combination the prior art references and since there is not a reasonable likelihood of success, Applicant respectfully requests that the above-noted obviousness rejection be withdrawn.

Conclusion

For the foregoing reasons, it is respectfully submitted the present application is in condition for allowance, and such action is earnestly solicited. The Examiner is invited to call the undersigned if there are any remaining issues to be discussed which could expedite the prosecution of the present application.

Respectfully submitted,

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